

REMARKS

Prior to entry of the present amendment, Claims 1-9 were pending and under consideration. In this amendment, Claim 2 is cancelled. Accordingly, following entry of the present amendment, Claims 1 and 3-9 will be pending and under consideration.

I. The Amendment to the Claims

The Claims have been amended, without prejudice, in order to more particularly point out and distinctly claim that which Applicants regard as their invention. In particular, Claim 2 is cancelled in the present amendment. The cancellation of Claim 2 does not present new matter, and is believed to place the claims in condition for allowance. Accordingly, Applicants respectfully request the entry of the amendment to the claims pursuant to 37 C.F.R. § 1.116.

II. Claim Objections

The PTO has objected to Claim 9 under 37 C.F.R. § 1.75 as an alleged substantial duplicate of Claim 2. Without acquiescing to the propriety of the objection, Applicants respectfully submit that the objection is moot in view of the cancellation of Claim 2. Accordingly, Applicants respectfully request that the objection to Claim 9 be withdrawn.

III. The Rejection of Claims 1-4 under the Judicially-Created Doctrine of Obviousness-Type Double Patenting

Claims 1-4 stand rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly obvious variants of Claims 1-4 of U.S. Patent No. 6,365,375 (“the ’375 patent”). Without acquiescing to the propriety of this rejection, Applicants submit herewith a Terminal Disclaimer disclaiming the terminal portion of a patent that issues from the present application to the extent that this patent extends beyond the expiration date of the ’375 patent. The rejection of the claims under the judicially-created doctrine of obviousness-type double patenting is thus overcome. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 1-4 under this doctrine.

IV. The Rejection of Claims 1-3, 6, and 9 under 35 U.S.C. § 102(b)

Claims 1-3, 6, and 9 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Casas *et al.*, 1996, *Biotechniques* 20(2):219-225 (“Casas”). Applicants respectfully

traverse the rejection of the claims as anticipated on the grounds that *Casas* does not teach each and every element of the rejected claims.

A. The Legal Standard

The standard governing anticipation under 35 U.S.C. § 102 requires strict identity. See M.P.E.P. § 2131. Thus, “for a prior art reference to anticipate in terms of § 102, every element of the claimed invention must be identically shown in a single reference.” *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir., 1990). Anticipation is not shown even when the differences between the claims and the cited reference are allegedly “insubstantial” and any missing elements could be supplied by the knowledge of one skilled in the art. *See Structural Rubber Prod. Co. v. Park Rubber Co.*, 223 U.S.P.Q. 1264 (Fed. Cir., 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253 (Fed. Cir., 1985), the Federal Circuit explained that even if the prior art teaches “substantially the same thing” as the claimed invention, the reference still cannot anticipate the invention. Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

B. The Claimed Invention

Claim 1 of the present application recites a method for the amplification of nucleic acid fragments from a sample, comprising first and second thermocyclic amplification reactions. The first amplification reaction is carried out using completely randomized primers, while the second amplification reaction is carried out using specific primers. The first and second amplification reactions are carried out using the same mixture of at least two DNA polymerases, at least one of which possesses 3'-5' exonuclease activity. In certain embodiments of the invention, for example, as recited by Claim 9, the temperature at which primer extension is carried out in the first amplification reaction is increased in at least some of the successive amplification cycles.

C. *Casas* does not Teach Each and Every Element of the Claimed Invention

In support of the rejection of the claims as anticipated by *Casas*, the PTO argues that this reference discloses each and every element of the invention as claimed. In particular, the PTO asserts that the two amplification reactions described in *Casas* were performed using the same mixture of DNA polymerases, and that the described amplification methods comprise an increase in temperature in at least some successive amplification cycles. Based, in part, on

these alleged teachings, the PTO argues that *Casas* discloses each and every element of the claimed invention and therefore anticipates Claims 1-3, 6, and 9.

In response, Applicants respectfully submit that *Casas* teaches neither use of the same two polymerases in the two amplification reactions nor an increase in the temperature at which primer extension is carried out in at least some amplification cycles of the first amplification reaction. With regard to which polymerases are used in the two amplification reactions, Applicants respectfully invite the PTO's attention to *Casas* at page 220, columns 1-2. Here, *Casas* describes three tested reaction mixtures for the first amplification reaction. Two of these reaction mixtures are simply not relevant to the present invention, as these reaction mixtures comprise only a single polymerase, not a mixture of two polymerases. See *Casas* at page 220, column 1, paragraphs 2 and 3, and at page 220, column 2, second full paragraph. The third reaction mixture comprises a mixture of *Taq* and *Pfu* DNA polymerases. See *Casas* at page 220, column 2, first full paragraph. In addition, at page 220, column 3, paragraph 2, *Casas* describes a second experiment to test the effects of the ratio of *Taq* DNA polymerase to *Pfu* DNA polymerase when using a mixture of DNA polymerases in a first amplification reaction.

However, *Casas* at page 221, column 1, first full paragraph, presents a single reaction mixture for a second amplification reaction. This reaction mixture contains only one polymerase, *Taq* DNA polymerase, not a mixture of two DNA polymerases. *Casas* does not describe any other reaction mixtures for use in the second amplification reaction. Thus, none of the experiments described in *Casas* use a mixture of polymerases in a second amplification reaction, let alone the same mixture as used in a first amplification reaction. Accordingly, *Casas* does not and cannot teach use of the same mixture of polymerases in both the first and second amplification reactions, as recited by, for example, Claim 1 of the present invention.

Furthermore, *Casas* does not teach an increase in the temperature at which primer extension is carried out in at least some amplification cycles of the first amplification reaction. Applicants respectfully invite the PTO's attention to *Casas* at page 220, column 3, paragraph 1. Here, *Casas* describes an amplification profile for the first amplification reaction, comprising 50 primer extension cycles. While the amplification profile does increase the temperature from the annealing step at 37°C to the primer extension step at 55°C, all of the polymerase extension (*i.e.*, primer extension) steps are performed at 55°C. Thus, the primer extension reaction of all of the cycles of the first amplification reaction described in *Casas* are performed at the same temperature, and the temperature at which the primer extension reaction is performed is not increased in any successive amplification cycles.

Accordingly, *Casas* does not teach an increase in the temperature of the primer extension reaction as recited by the presently claimed invention.

As shown by the foregoing, *Casas* does not teach each and every element of the invention as presently claimed. Therefore, Applicants respectfully submit that *Casas* does not anticipate Claims 1-3, 6, and 9, and earnestly request that the rejection of these claims under 35 U.S.C. § 102(b) be withdrawn.

V. The Rejection of Claims 4-5 and 7-8 as Obvious under 35 § U.S.C. 103(a)

Claims 4-5 stand rejected as obvious under 35 § U.S.C. 103(a) over *Casas* in view of *Ando et al.*, 1997, *J. Clin. Microbiol.* 35(3):570-577 (“*Ando*”), while Claims 7-8 stand rejected as obvious over *Casas* in view of *Von Eggeling et al.*, 1997, *Hum. Genet.* 99:266-270 (“*Von Eggeling*”). Applicants respectfully traverse the rejection on the grounds the PTO has not presented a *prima facie* case for obviousness in that the combined references do not disclose each and every element of the invention as presently claimed.

A. The Legal Standard

To reject a claim under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide “motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant.” *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51U.S.P.Q.2d 1386 (Fed.Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow*

Chemical, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. The Cited References do not Teach or Suggest Each and Every Element of the Claimed Invention

The PTO supports the rejection of Claims 4-5 and 7-8, in part, on the same portions of *Casas* as were cited in the rejection of Claims 1-3, 6, and 9 as anticipated. In particular, the PTO relies upon *Casas* to provide the teaching or suggestion to use the same mixture of polymerases in both amplification reactions and to increase the temperature at which primer extension is carried out in at least some subsequent amplification cycles.

As shown above, *Casas* does not teach or suggest either using the same mixture of polymerases for both amplification reactions or increasing the temperature at which primer extension is carried out in at least some subsequent amplification cycles. Therefore, the cited references, even if they could be validly combined, do not teach each and every element of Claims 4-5 and 7-8. Accordingly, Applicants respectfully submit that the rejection of these claims as obvious over *Casas* in view of either *Ando* or *Von Eggeling* is erroneous and respectfully request its withdrawal.

VI. Finality of the Office Action Mailed March 14, 2003

Applicants respectfully disagree that new grounds of rejection presented in the final Office Action mailed March 14, 2003, were necessitated by Applicants' amendments in the response filed December 17, 2002. The new rejections would have been equally well-founded with the claims pending prior to the previous amendment, and could have been made in the first Office Action. *See* MPEP § 706.07(a). Accordingly, Applicants respectfully request that the finality of the Office Action mailed March 14, 2003, be withdrawn and the present amendment be entered and considered pursuant to 37 C.F.R. § 1.111 rather than 37 C.F.R. § 1.116.

CONCLUSION

In view of the foregoing amendment and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935. The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 (order no. 1803-330-999) for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: July 14, 2003

 42,983
Rahul Pathak (Reg. No.)
For: Nikolaos C. George (39,201)
PENNIE & EDMONDS LLP
3300 Hillview Avenue
Palo Alto, California 94304
(650) 493-4935